ORIGINAL ARTICLE

Effects of triple combination of hydrocortisone, thiamine, and Vitamin C on clinical outcome in patients with septic shock: A single-center randomized controlled trial

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Background: Recent studies suggest that hydrocortisone, Vitamin C, and thiamine alone or in combination may improve the clinical outcomes of patients with septic shock. The aim of this study is the effects of this combination therapy on clinical outcome and sepsis biomarkers in patients with septic shock. **Materials and Methods:** Fifty-eight consecutive patients suffering septic shock were randomly assigned into two groups receiving the combination therapy of hydrocortisone (50 mg/6 h, intravenously), Vitamin C (1.5 g/6 h in 100 ml normal saline or DW5%, intravenously), and thiamine (200 mg/12 h in 50 ml normal saline or DW5%, intravenously) or placebo for up to 4 days. **Results:** The decline in procalcitonin, lactate, and leukocyte count 72 h after the initiation of treatment was significantly greater in the intervention as compared to the control group. The intervention group has a significantly lower sequential organ failure assessment score 72 h after treatment ($P < 0.001$). The mean duration of vasopressor dependency was shorter in the intervention group ($P = 0.039$). In-hospital death occurred in 10.3% of the patients who received combination therapy and 37.9% in the control group ($P = 0.014$). **Conclusion:** The administration of the triple combination of hydrocortisone, thiamine, and Vitamin C appeared to be effective in improving the clinical outcomes of patients with septic shock and of reducing vasopressor requirements with a significant increase in the rate of improvement of sepsis biomarkers.

Key words: Biomarkers, hydrocortisone, randomized controlled trial, septic shock, thiamine, Vitamin C

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INTRODUCTION

Sepsis is a life-threatening disorder caused by immune dysfunction in response to various infecting pathogens.[1] Secondary hemodynamic instability due to vasodilatation, disturbances of coagulation, and fibrinolysis and endothelial dysfunction are key factors resulting organ damage in patients with sepsis.[2] In the United States, epidemiological studies suggest that the incidence of sepsis varies from 900,000 to 3,000,000 cases/per year.[3] The mortality rate of sepsis varies from 14.7% to 30% in children and adolescents[4] and up to 45% in adults. Although the mortality rate from sepsis in developed nations has been declining in recent years, its incidence is increasing;[5] consequently, the burden of this disease enormous.

The sympathetic nervous system and hypothalamic-pituitary-adrenal axis is activated by stressors such as sepsis, resulting in the release of endogenous catecholamines and cortisol from the adrenal glands[6] Cortisol is an endogenous glucocoricoid that reduces the production of various inflammatory cytokines by inhibiting nuclear-factor κB.[7,8] Cortisol has additional physiological effects such as increasing blood glucose

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levels by inducing liver gluconeogenesis and reducing peripheral glucose reabsorption, as well as increasing blood pressure by increasing sensitivity to catecholamines. Corticosteroids are synthetic drugs, which have similar biological properties to cortisol. Recent data suggest that low-dose hydrocortisone may reduce the mortality of patients with septic shock.[9,10] While there is controversy regarding the mortality reduction of corticosteroids in patients with septic shock, these drugs have been demonstrated to reduce vasopressor dependency and the duration of mechanical ventilation.[11]

Thiamine is a cofactor for a variety of cellular enzymes, which are essential for carbohydrate metabolism, oxidative mitochondrial phosphorylation, and the synthesis of adenosine triphosphate.[12,13] Despite its importance, the body is not able to produce thiamine and stores only 30 mg of it in tissues such as skeletal muscle, heart, kidneys, and brain.[14] Thiamine deficiency occurs within 2 weeks of marginal intake. Thiamine deficiency is common in patients with sepsis.[15] Various factors contribute to the deficiency of thiamine in patients with sepsis, including reduced intake, diarrhea, malnutrition, and increased metabolic utilization.[16] In an experimental sepsis model, thiamine deficiency was associated with oxidative stress and inflammatory changes.[17] Despite the high prevalence of thiamine deficiency in sepsis, the beneficial effects of thiamine supplementation are unclear.

Vitamin C is a water-soluble vitamin that plays a key role in biosynthetic and metabolic processes.[18] It is a potent antioxidant that reduces the damaging effects of oxygen radicals.[19] Vitamin C is required for normal functioning of the immune system and is an essential co-enzyme for many biological reactions. Vitamin C is involved in reducing the pro-inflammatory and pro-coagulation factors that cause organ damage from ischemia.[20] Vitamin C improves endothelial dysfunction by reducing the production of free oxygen radicals.[21] In addition, laboratory studies have shown that Vitamin C reduces platelet adhesion,[22] prevents hypothalamic neuronal damage, limits oxidative phagocyte damage, improves immune cell function and increases the synthesis of endogenous catecholamines.[23] Patients with septic shock typically have very low Vitamin C levels.[24]

Recently, some studies have shown the beneficial effects of hydrocortisone, thiamine, and Vitamin C in improving the clinical outcomes of sepsis and septic shock.[25] The aim of the present study was to assess the effects of combination therapy including hydrocortisone, thiamine, and Vitamin C on clinical outcome as well as biomarkers in patients with septic shock referred to an intensive care unit (ICU).

MATERIALS AND METHODS

Design and setting

In this randomized controlled trial (RCT), consecutive patients suffering septic shock (intubated with mean systolic blood pressure lower than 65 mmHg) who were referred to ICUs in Ayatollah Mousavi, a general hospital in Zanjan, Iran, between May and November 2018 were included into the study. The research protocol was reviewed and approved by the University Review Board in Center for Development of Clinical Research of Ayatollah Mousavi Hospital and Hospital Ethics Committee affiliated with the university (decree code: A-11-328-21) and IRCT20150825023760N7 code accepted on February, 22 2019, which corroborated its ethical considerations in line with Declaration of Helsinki 1995, revised 2018.[26] Patients were hospitalized or died in the ICU for <72 h, patients <18 years of age and patients with therapeutic limitations were excluded.

Medication interference

After obtaining written informed consent, the 58 subjects were randomly assigned (using the computerized number random table) into two groups receiving the assessed combination therapy including hydrocortisone (50 mg/6 h, intravenously) (It was injected at 10 am, 4 pm, 10 pm, and 4 am), Vitamin C (1.5 g/6 h in 100 ml normal saline, intravenously) (It was infused at 10 am, 4 pm, 10 pm, and 4 am), and thiamine (200 mg/12 h in 50 ml normal saline, intravenously) (It was infused at 6 AM and 12 PM) in intervention group.[27] Patients were treated for 3 days during ICU admission. Given the sensitivity of the study population, a nurse, MT, performed the intervention for patients with injecting of drugs and anesthesiology residents collecting the data.

The overall treatment of sepsis was performed according to the sepsis guideline and ICU care protocols were considered as antibiotic therapy, prophylaxis of deep venous thrombosis, sedative medications, mechanical ventilation, and prescription of vasopressor.[28] The study endpoint was the change in serum levels of pro-calcitonin, lactate, and leukocyte count after 72 h of treatment in both the groups. In-hospital mortality and change in the sequential organ failure assessment (SOFA) score was also determined and compared across the two groups.

Ethical considerations

1. Obtaining Ethics Code from the Ethics Committee of Zanjan University of Medical Sciences
2. Obtaining letter of reference from Zanjan University of Medical Sciences
3. Obtaining informed consent from the participant's family

4. Conducting the triple therapy in the control group after completing the study.

Statistical analyses

Descriptive analysis was used to describe the data, including mean ± standard deviation for quantitative variables and frequency (percentage) for categorical variables. Chi-square test, independent *t*-test or Mann–Whitney U test were used for comparison of variables. The difference in mortality between the intervention and control group was assessed using the multivariable logistic regression analysis with the presence of the baseline variables. For the statistical analysis, the statistical software IBM SPSS Statistics for Windows version 20.0 (IBM Corp. Released 2013 was used, Armonk, New York, USA) was used. $P < 0.05$ was considered statistically significant.

RESULTS

Fifty-eight consecutive patients suffering from septic shock were included in this study. All patients were intubated; the acute physiology, age, chronic health evaluation II score was 18.79 ± 1.54 in treatment group and 18.41 ± 1.72 in control group ($P = 0.381$); aged ranged from 18 to 70 years and serum pro-calcitonin level ≥2 ng/ml in all patients. The baseline characteristics of the two groups are presented in Table 1. The main reason for developing septic shock in both the intervention and control groups included multiple trauma (69.0% versus 89.7%), while other less common etiologies for septic shock included suicide by fire, stabbing or hanging, pneumonia and toxic megacolon. There was no statistical difference in the reasons for septic shock between the two groups ($P = 0.173$). The most common underlying disorders were hypertension (27/5% vs. 24.1%, $P = 0.256$) and Type II diabetes mellitus (6/8% vs. 6.9%, $P = 0.389$). As shown in Table 2, the baseline values of biomarkers including pro-calcitonin, lactate, and leukocyte count were similar in both groups; however, the levels of these markers fell to a significantly greater degree in the intervention group as compared to control group 72 h after initiation of treatment. Similarly, the sequential organ failure score (SOFA) was similar in both groups at baseline (4.59 ± 1.48 vs. 5.31 ± 1.63, $P = 0.081$), however, the group receiving combination therapy demonstrated a lower SOFA score 72 h after treatment (1.52 ± 1.18 vs. 3.03 ± 1.27, $P < 0.001$). The mean duration of vasopressor support in combination and groups were 11.66 ± 17.21 h and 23.45 ± 24.53 h, respectively ($P = 0.039$).

In-hospital death occurred in 10.3% of the patients who received combination therapy versus 37.9% in control group ($P = 0.014$). Based on the multivariable logistic regression model with the presence of baseline variables including gender, age, marital status, education, administration of the combination therapy was associated with a significant reduction in-hospital death in patients with septic shock (Odds Ratio = 11.638, $P = 0.011$) [Table 3].

No Vitamin C, hydrocortisone, and thiamine-related adverse effect were identified in the intervention group during the study.

DISCUSSION

These compounds may positively influence the pathophysiologic derangements of sepsis through numerous processes, including the reduction of inflammatory processes, inhibiting the production of oxidative stress, improving the synthesis of endogenous vasoconstrictors, and improving endothelial function. Our study demonstrated that the triple combination of these drugs improved the clinical outcome of patients with septic shock (more rapid improvement in SOFA scores, reduced requirement for vasopressor agents with a significant reduction in the risk of hospital mortality) as well as laboratory markers associated with the pathogenesis of sepsis. We have demonstrated that the combination of hydrocortisone, Vitamin C and thiamine in the dosages as reported by Marik *et al*. was safe and effective in attenuating the organ injury associated with sepsis and in reducing hospital mortality.[27] The results of our RCT are quite similar to that of the before-after study reported by Marik *et al*. who reported a more rapid improvement in the SOFA score and a reduction in mortality from 40.4% to 8.5% in the treatment group. Finally, in the study by Marik *et al*., the mean duration of use of the vasopressor in the Vitamin C group was significantly shorter than the control group, which was consistent with our findings.[27] In Paul Marik's study, the need for DELTA SOFA72-h hemodialysis was also calculated which was not done in this study due to time constraints.

Recently, Annane *et al*. demonstrated that the combination of hydrocortisone and fludrocortisone reduced the mortality of patients with refractory septic shock.[29] However, the ADRENAL study which enrolled septic shock patients with a lower severity of illness failed to replicate these findings, suggesting that only the sickest patients benefit from corticosteroids.[30] Zabet *et al*. evaluated the use of Vitamin C (25 mg/kg q 6 for 72 h) in surgical patients with septic shock. The patients in the study by Zabet *et al*. were sicker than those in our study (baseline SOFA score of about 12 vs. 5).[31] These authors reported a significant reduction in 28-day mortality with Vitamin C mono-therapy (64.2% vs. 14.2%, $P = 0.009$) together with a significant reduction in the use of vasopressor agents. These data suggest that corticosteroid and Vitamin C mono-therapy may only be of benefit in the sickest subset of patients. Donnino *et al*. evaluated the role of

Table 1: Baseline characteristics of study population

Item	Intervention group (*n*=29), *n* (%)	Control group (*n*=29), *n* (%)	*P*
Gender			
Male	21 (72.4)	26 (89.7)	0/094
Female	8 (27.6)	3 (10.3)	
Mean age, years±SD	45.4±19.8	45.4±15.8	0/999
Education			
Illiterate	18 (62.1)	25 (86.2)	0/070*
Elementary	1 (3.4)	2 (6.9)	
Diploma	8 (27.6)	2 (6.9)	
College education	2 (6.9)	0 (0.00)	
Marital status			
Married	21 (72.4)	24 (82.8)	0/345
Single	8 (27.6)	5 (17.2)	
Etiology of septic shock			
Multiple trauma	20 (69.0)	26 (89.7)	0/055*
Seizures, hydrocephalus and cerebral hemorrhage	5 (17.2)	0 (0.00)	
Etc. (suicide by fire, stabbing or hanging, pneumonia and toxic megacolon)	4 (13.8)	3 (10.3)	
Underlying disease			
Hypertension	8 (27.5)	7 (24.1)	0/155*
Diabetes mellitus	2 (6.8)	2 (6.9)	
Ischemic heart disease	1 (3.4)	0 (0.0)	
Convulsions, types of tumors, paraplegia	2 (6.9)	6 (20.7)	
Kidney injury	3 (10.3)	0 (0.0)	
No underlying disease	13 (44.8)	14 (48.3)	

*Fisher exact test. SD=Standard deviation

Table 2: The change in clinical and laboratory markers following treatment

Item	Intervention group (*n*=29)	Control group (*n*=29)	*P*
APACHE II	18.79±1.54	18.41±1.72	0.381
Pro-calcitonin (ng/ml)			
Baseline	8.06±3.45	6.38±4.23	0.101
72 h after	2.66±2.54	4.77±3.74	0.015
Lactate (mmol/l)			
Baseline	13.5±4.5	12.9±8.6	0.739
72 h after	4.6±2.8	7.9±5.5	0.008
Leukocyte count (1.9× 10^9/L)			
Baseline	19,331.0±4780.2	17,900.00±4840.23	0.262
72 h after	9024.1±4258.4	12,737.93±3788.65	0.001
SOFA score			
Baseline	4.5±1.4	5.3±1.6	0.081
72 h after	1.5±1.1	3.0±1.2	<0.001
Time to receiving vasopressor (h)	11.66±17.21	23.45±24.53	0.039

SOFA=Sequential organ failure score; APACHE II=Acute physiology, age, chronic health evaluation II

Table 3: Multivariable logistic regression model to assess effect of triple therapy on in-hospital death

Variable	β	SE	*P*	OR
Triple therapy	2.454	0.968	0.011	11.638
Age	0.016	0.027	0.539	1.017
Gender	1.736	1.074	0.106	5.675
Marital status	20.375	1.038	0.998	0.001
Education	0.718	0.503	0.153	2.051

OR=Odds ratio; SE=Standard error

intravenous thiamine in patients with septic shock.[32] These authors demonstrated a reduction of mortality in the subset of patients who were thiamine deficient.[33] The results of our study as well as that of Marik *et al.*, suggest that all patients with sepsis (regardless of illness severity) are likely to benefit from combination therapy with hydrocortisone, Vitamin C, and thiamine.[27] Ongoing RCTs, which are evaluating different combinations of these agents in varying populations of patients with sepsis, should provide data to answer these important questions. Finally, it should be noted that in order to achieve the greatest therapeutic benefit, determination of the optimal dosage, and timing of the administration of each agent is required.

The major limitation of our study is the small sample size and the fact that this is a single-center study. However, we believe this to be the first RCT to evaluate the triple combination therapy. Furthermore, the results of our study are consistent with previously published studies.

CONCLUSION

In this study, we have demonstrated that the administration of a triple combination of hydrocortisone, thiamine, and Vitamin C is effective in improving the clinical outcomes of patients with septic shock. It may soon be time to consider this safe and cheap adjunctive therapy as a routine in the management of critically ill patients with sepsis.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al*. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315:801-10.
2. Vincent JL, De Backer D. Circulatory shock. N Engl J Med 2013;369:1726-34.
3. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med 2013;41:1167-74.
4. Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, *et al*. Global epidemiology of pediatric severe sepsis: The sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med 2015;191:1147-57.
5. Stevenson EK, Rubenstein AR, Radin GT, Wiener RS, Walkey AJ. Two decades of mortality trends among patients with severe sepsis: A comparative meta-analysis. Crit Care Med 2014;42:625-31.
6. O'connor TM, O'halloran DJ, Shanahan F. The stress response and the hypothalamic-pituitary-adrenal axis: From molecule to melancholia. Q J Med 2000;93:323-33.
7. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol 2011;335:2-13.
8. Cruz-Topete D, Cidlowski JA. One hormone, two actions: Anti- and pro-inflammatory effects of glucocorticoids. Neuroimmunomodulation 2015;22:20-32.
9. Sbertoli R, Hu Z, Henke J, Wu E, Santosh S, Osmon S, *et al*. Effect of very low-dose hydrocortisone on shock reversal in patients with septic shock. Crit Care Explor 2020;2:e0096.
10. Lian XJ, Huang DZ, Cao YS, Wei YX, Lian ZZ, Qin TH, *et al*. Reevaluating the Role of corticosteroids in septic shock: An updated meta-analysis of randomized controlled trials. Biomed Res Int 2019;2019:3175047.
11. Hermans G, Agten A, Testelmans D, Decramer M, Gayan-Ramirez G. Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: A prospective observational study. Crit Care 2010;14:R127.
12. Tylicki A, Łotowski Z, Siemieniuk M, Ratkiewicz A. Thiamine and selected thiamine antivitamins - biological activity and methods of synthesis. Biosci Rep 2018;38:1-23.
13. Dhir S, Tarasenko M, Napoli E, Giulivi C. Neurological, psychiatric, and biochemical aspects of thiamine deficiency in children and adults. Front Psychiatry 2019;10:207.
14. Depeint F, Bruce WR, Shangari N, Mehta R, O'Brien PJ. Mitochondrial function and toxicity: Role of the B vitamin family on mitochondrial energy metabolism. Chem Biol Interact 2006;163:94-112.
15. Mallat J, Lemyze M, Thevenin D. Do not forget to give thiamine to your septic shock patient! J Thorac Dis 2016;8:1062-6.
16. Hiffler L, Rakotoambinina B, Lafferty N, Martinez Garcia D. Thiamine deficiency in tropical pediatrics: New insights into a neglected but vital metabolic challenge. Front Nutr 2016;3:16.
17. de Andrade JA, Gayer CR, Nogueira NP, Paes MC, Bastos VL, Neto JD, *et al*. The effect of thiamine deficiency on inflammation, oxidative stress and cellular migration in an experimental model of sepsis. J Inflamm (Lond) 2014;11:11.
18. Spoelstra-de Man AM, Elbers PW, Oudemans-Van Straaten HM. Vitamin C: Should we supplement? Curr Opin Crit Care 2018;24:248-55.
19. Mandl J, Szarka A, Bánhegyi G. Vitamin C: Update on physiology and pharmacology. Br J Pharmacol 2009;157:1097-110.
20. Fisher BJ, Seropian IM, Kraskauskas D, Thakkar JN, Voelkel NF, Fowler AA 3rd, *et al*. Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury. Crit Care Med 2011;39:1454-60.
21. Rodemeister S, Biesalski HK. There's life in the old dog yet: Vitamin C as a therapeutic option in endothelial dysfunction. Crit Care 2014;18:461.
22. Secor D, Swarbreck S, Ellis CG, Sharpe MD, Tyml K. Ascorbate reduces mouse platelet aggregation and surface P-selectin expression in an *ex vivo* model of sepsis. Microcirculation 2013;20:502-10.
23. Wilson JX. Mechanism of action of vitamin C in sepsis: Ascorbate modulates redox signaling in endothelium. Biofactors 2009;35:5-13.
24. Zhao Y, Ding C. Effects of hydrocortisone on regulating inflammation, hemodynamic stability, and preventing shock in severe sepsis patients. Med Sci Monit 2018;24:3612-9.
25. Moskowitz A, Andersen LW, Huang DT, Berg KM, Grossestreuer AV, Marik PE, *et al*. Ascorbic acid, corticosteroids, and thiamine in sepsis: A review of the biologic rationale and the present state of clinical evaluation. Crit Care 2018;22:283.
26. World Medical Association. Issue information-declaration of Helsinki. J Bone Miner Res 2018;33:1-2.
27. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C, and thiamine for the treatment of severe sepsis and septic shock: A retrospective before-after study. Chest 2017;151:1229-38.
28. Plevin R, Callcut R. Update in sepsis guidelines: What is really new? Trauma Surg Acute Care Open 2017;2:e000088.
29. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, *et al*. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med 2018;378:809-18.
30. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, *et al*. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 2018;378:797-808.

31. Zabet MH, Mohammadi M, Ramezani M, Khalili H. Effect of high-dose ascorbic acid on vasopressor's requirement in septic shock. J Res Pharm Pract 2016;5:94-100.
32. Donnino MW, Andersen LW, Chase M, Berg KM, Tidswell M, Giberson T, *et al*. Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: A pilot study. Crit Care Med 2016;44:360-7.
33. Holmberg MJ, Moskowitz A, Patel PV, Grossestreuer AV, Uber A, Stankovic N, *et al*. Thiamine in septic shock patients with alcohol use disorders: An observational pilot study. J Crit Care 2018;43:61-4.